REMARKS

Upon entry of the foregoing amendments, claims 3-11 will be pending, claim 3 being the only independent claim.

Response to Restriction Requirement

At paragraphs 2 through 6, the Office Action included a seven-way restriction requirement, specifically set forth in paragraph 2 at page 2. Applicants hereby elect for prosecution in this application, without traverse, the invention of Group I, directed to quinazolines, wherein in the compound of Formula (I) of original claim 1, $X_1=X_2=X_3=X_4$=carbon. This election is made without prejudice to the filing of any of the other asserted inventions in one or more related applications. This election confirms the provisional election made by Applicants' former attorney Thomas J. Dodd on May 13, 2004, during a telephone conversation with the Examiner.

New independent claim 3 has revised the formula of the present invention, identified as Formula Ib, to include only the elected invention. Therefore, all pending claims in the application are directed only to the elected subject matter.

Amendment to the Title

Paragraph 7 of the Office Action objected to the title and suggested a more descriptive title of the invention. The suggested title was substantially adopted, except that "and Related" was included before "Antifolates." Applicants believe that the title is now descriptive of the subject matter claimed in this application. Reconsideration and withdrawal of this objection are respectfully requested.

Amendment to the Abstract

Paragraph 8 of the Office Action objected to the Abstract as too short and generic. Accordingly, the Abstract has been amended to read substantially the same as amended claim 1, except for a slightly different preamble and the lead-in clause relating to the improvement to the process. Applicants believe that the Abstract is now satisfactory. Reconsideration and withdrawal of this objection are respectfully requested.

Explanation of the Amendments to the Written Description and Their Support

While reviewing the application, it was noticed that several corrections were needed to the written description portion of the application to correct inadvertent errors relating to nomenclature, structural formulas, citations of references, and to make the structural formulas consistent throughout the written description and claims, particularly with respect to the various R groups. No new matter has been added.

More specifically, the title of MDAM at page 1, lines 5-6 has been corrected to indicate that it is a gamma compound, rather than a lamda compound, consistent with the nomenclature and general structure mentioned in the first paragraph at page 3 of the application.

The first two structures at page 2 have been corrected. The folic acid structure had too many bonds at the carbonyl carbon and the nitrogen bridging the quinazoline and benzoyl groups should be NH. These corrections have been made. The second structure, relating to MTX or ATM depending on the R group, has been amended to indicate that the bond to the 4-amino group should be to the nitrogen atom, rather than to the hydrogen atoms.

The citations in lines 1 and 5 at page 5 of the application, and at page 6, line 5 of the application, have been corrected to delete the italics for the U.S. patent and to recite the issue number of the journal article.

Formula I at page 6 has been corrected to more clearly show the double bond between X_1 and X_2, and R_1 has been changed to R_a to avoid confusion with respect to other definitions for R_1 later in the application and in the claims. As suggested in paragraph 12 of the Office Action, X_3 and X_4 have been re-defined to take into account appropriate valences, such that X_3 and X_4 are each individually CH or nitrogen.

Formula Ia at page 7 has been amended to be consistent with claim 1 as originally filed. When R_4 is bonded directly to the phenyl group, as shown in the amended structure, R_4 can no longer be hydroxy or alkoxy, but rather, hydroxy and alkoxy are definitions, among others, for X in the definition of R_4. X_3 and X_4 have been re-defined as explained above concerning Formula I.

Spelling corrections to the word "liter" were made at page 14, line 3, page 15, line 3, and page 18, line 15.

that modified Horner reagent to produce the compound of Formula Ib. One skilled in the art would have no motivation to revise Nair's process to Applicants' improved process without a teaching or even a hint to do so, other than the hindsight provided in the present application, which cannot be relied upon as support for a rejection. Accordingly, reconsideration and withdrawal of the obviousness rejection in view of Nair is respectfully solicited.

Paragraph 21 of the Office Action is a provisional double patenting rejection based on claim 1 of copending Application No. 10/627,485, assigned to the assignee of the present application. In view of the amendments to the claims of the present application, it is believed that the double patenting rejection is also overcome. Reconsideration and withdrawal of the double patenting rejection is respectfully solicited.

Conclusion

Accompanying this Amendment is an Information Disclosure Statement including two references for consideration by the Examiner. The references are not believed to render the presently claimed invention unpatentable.

Also accompanying this Amendment is a Revocation and Appointment of Attorney by Assignee. Mr. Dodd, former in-house Senior Patent Counsel for Applicants' assignee, is no longer employed by the assignee. Accordingly, until further notice, further communications should be directed to the undersigned attorney. If advancement of the prosecution of this application could be enhanced by a telephone conference between the Examiner and the undersigned attorney, the Examiner is invited to so contact the undersigned attorney at the Examiner's convenience.

A review of the amendments to the written description reveals that no new matter has been added. Accordingly, Applicants respectfully solicit the entry of the amendments to the written description.

Claim Rejections Under 35 U.S.C. § 112, second paragraph

Applicants have amended the claims to focus on the elected invention and to clarify the subject matter sought to be protected in this application. Independent claim 3 has been written in a Jepson format to better indicate the improvement in the process, focusing on the reactions of the type shown in Examples 5 and 6. The claims are supported by the application as filed as set forth in the reaction Schemes 1 and 2, the paragraph bridging pages 11 and 12, and/or the Examples, particularly Examples 5 through 10. See also page 8, lines 8-9, referring to a *p*-benzoic acid alkylene moiety, and page 9, lines 4-8, referring to the coupling reaction. Again, no new matter has been added. The amendments of the claims also overcome the rejections based on 35 U.S.C. § 112, second paragraph and those based on prior art. Accordingly, reconsideration and withdrawal of those rejections are respectfully solicited.

The compound of Formula Ib in claim 3 has been amended to be consistent with Formula Ia, wherein X_1=X_2=carbon and X_3 and X_4=CH, as elected. All of the R groups are defined in a manner consistent with the like R groups elsewhere in the application.

Double bonds are shown as and where appropriate.

In the definition of R_1 and R_2, the phrase "or a nitrogen or oxygen protecting group" has been retained, even though paragraph 10 of the Office Action indicated that this phrase would be considered indefinite. Although neither a nitrogen protecting group nor an oxygen protecting group is specifically shown by example in the application, Applicants respectfully submit that such terms are very well known to those skilled in the art, namely graduate chemists. Protecting groups, also called "protective groups," are simply groups that prevent the undesired reaction of the protected group, here a nitrogen or an oxygen, in such groups as amino groups or hydroxyl groups, before reaction therewith is intended. Enclosed are copies of the title page and pages 17-200 and 495-653 of T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis," 3rd Edition, John Wiley & Sons, Inc. (1999). This well-known textbook provides a great many examples of suitable nitrogen or oxygen protecting groups. The Examiner's attention is specifically directed to pages 17-20, 495, 496 and 500-502, wherein particularly effective

protecting groups for use in the presently claimed invention are identified by checkmarks and would be well known to those skilled in the art. Details about the checked protecting groups are set forth at the indicated pages of Greene *et al.* Since the written description of the patent application is directed to one skilled in the art (35 U.S.C. § 112, second paragraph), Applicants respectfully submit that these groups and their use would be so well known to those skilled in the art that the inclusion of the phrase "or a nitrogen or oxygen protecting group" is not indefinite.

Responding further to the specific issues raised in paragraph 10 of the Office Action, the protecting groups used in the present application, as would be apparent to a skilled chemist in view of the reactions that take place, are preferably at least base-stable. The protecting groups are attached through nitrogen and oxygen, rather than directly to the pyrimidine ring. One skilled in the art would realize that R_1 and R_2 may be $-C(O)-OBu^t$ or $-CH_2C_6H_5$ when the protecting group is BOC or Bzl, if those reagents are used in the reaction schemes.

In view of the foregoing explanation, Applicants respectfully request the Examiner to reconsider and withdraw the rejection based on the use of the term "or a nitrogen or oxygen protecting group."

Paragraph 11 of the Office Action rejected the original claims under 35 U.S.C. § 112, second paragraph as being indefinite with respect to the recitation of "an amino acid residue." An issue was raised concerning examples other than glutamic acid and aspartic acid with questions about whether the twenty natural amino acids coded by DNA and carboxylic acids with an amino group in the α-position were intended. The Office Action further raised issues about all organic acid residues containing an amino group somewhere in the molecule including acids of sulfur, phosphorous and boron, along with an inquiry as to how the residue is attached to C(O)-, as being through the amino group or attached anywhere.

The Examiner's attention is directed to the paragraph bridging pages 6 and 7, relating to preferred amino acids, and particularly to page 7, lines 1-2, stating "other amino acids may also be employed" besides the glutamic acid and aspartic acid, and particularly their naturally occurring L-enantiomers. Thus, the twenty natural amino acids coded by DNA are intended, as are carboxylic acids with an amino group in the α-position. Likewise, those skilled in the art would realize that organic acid residues containing an amino group located within the residue at a position appropriate to be coupled, such as those including phosphorous, as in residues of phosphoric acid, could also be used. Residues of amino acids would be attached to the C(O)-

group through the amino group. Applicants respectfully submit that one skilled in the art would realize, without undue experimentation, in view of the written description, which amino acid residues could be used and how to do so. Accordingly, reconsideration and withdrawal of this rejection are respectfully solicited.

Paragraph 12 of the Office Action rejected the claims under 35 U.S.C. § 112, second paragraph, as being indefinite with respect to the definition of X_1, X_2, X_3 and X_4. The Examiner pointed out unsatisfied valences for these variables. In view of the election set forth above, Formula Ib in claim 3 no longer includes these variables. Moreover, these variables were amended as suggested by the Examiner with respect to the structure of Formula I at page 6 and Formula Ia at page 7 in the written description. Accordingly, this rejection is now moot with respect to the presently pending claims.

Paragraphs 13 and 14 of the Office Action rejected the original claims under 35 U.S.C. § 112, second paragraph, as being indefinite with respect to the phrase "a starting reagent capable of being cyclized to a 2,4-disubstituted fused aromatic nitrogen-containing heterocycle." This phrase is no longer used in independent claim 3 or any other claim of the application. Accordingly, this rejection is now moot.

Paragraph 15 of the Office Action rejected the original claims under 35 U.S.C. § 112, second paragraph, as being indefinite with respect to the use of the phrase "a reactive moiety." This phrase is no longer used in independent claim 3 or any other claim in the application. Accordingly, this rejection is also moot.

Paragraph 16 of the Office Action rejected the original claims under 35 U.S.C. § 112, second paragraph, as being indefinite with respect to the phrases "the 4-substituted moiety" and the "4-substituted aromatic ring fragment." Since these terms are no longer used in claim 3 or any other claim in the application, this rejection is moot.

Paragraph 17 of the Office Action rejected claim 2 under 35 U.S.C. § 112, second paragraph with respect to the use of the phrase "the reactive moiety is a nitrogen based leaving group." This phrase is no longer used in claim 3 or any other claim in the application. Therefore, this rejection is also moot.

Applicants respectfully submit that new claims 3-11 fully comply with 35 U.S.C. § 112, second paragraph.

Claim Rejections Under 35 U.S.C. § 102

Paragraph 18 of the Office Action rejected the original claims under 35 U.S.C. § 102(b) as being anticipated by Yan, the Examiner taking the position that the Formula I compound was disclosed in Yan, as was the reaction scheme as set forth at page 541-543 of Yan.

Applicants respectfully traverse the rejection as it may be applied to claim 3 and any other claim for the following reasons.

Independent claim 3 focuses the present invention on the improvement in a process for synthesizing a compound of Formula Ib. The improvement comprises steps after the starting materials and certain intermediates are converted to a 2,4-diamino-6-formyl-quinazoline. Yan, at page 542, the second paragraph of the left column, discloses using a Wittig condensation with phosphonium bromide as the Wittig salt, and using NaH as the base in DMF solvent. Yan's reaction scheme is believed to be not scalable because the by-product of the Wittig salt is triphenyl phosphine oxide, which is organically insoluble, leading to contamination, as it is not soluble in aqueous media. Moreover, since the Wittig salt is unstable, it cannot be scaled up and stored.

In contrast to Yan, the present invention uses a modified Horner reagent which is scalable in high purity without contamination. The modified Horner reagent in the present application is triethyl phosphite. References to a modified Horner reaction are set forth in the last paragraph at page 11, and the particular reaction scheme is set forth in Example 5 bridging pages 16 and 17. Triethyl phosphite is specifically mentioned at page 17, line 2. Unlike the Wittig salt of Yan, triethyl phosphite is a liquid which is easily evaporatable or distillable. The by-products of the reaction using the triethyl phosphite as the reagent do not result in insoluble contamination as with a Wittig salt. The ethyl phosphite by-products are highly water soluble and easily removable. They are stable and therefore, scalable and may be stored for later use. The resulting intermediate shown in the reaction scheme at the beginning of Example 5 at the bottom of page 16 is a novel compound, to Applicants' knowledge. Likewise, the intermediate claimed in claim 3 as "4-R_4-carbonyloxyalkyl-phenyl-alkyldiethylphosphite" is also believed to represent a new class of compounds. Yan does not disclose or suggest this reaction or these compounds.

The final step in the improved process now claimed in claim 3 of the application reacts the 4- R_4-carbonyloxyalkyl-phenyl-alkyldiethylphosphite with 2,4-diamino-6-formyl-quinazoline to form the compound of Formula Ib. Since the novel intermediate is not disclosed or suggested

in Yan, there is also no disclosure of using it to react with the quinazoline to form the desired compound of Formula Ib. Accordingly, reconsideration and withdrawal of the rejection as it may be applied to any of the new claims is respectfully solicited.

Paragraph 19 of the Office Action referred to three other references which were indicated as being merely cumulative to Yan, namely Oatis, Harris and Vaidya.

The three references deemed in the Office Action to be cumulative to Yan neither anticipate nor render the presently claimed invention obvious. Oatis does not use a triethyl phosphite modified Horner reagent in any of its Schemes I, II or III as set forth at pages 1393 or 1394. Scheme I uses a methylene sulfide bridge between the quinazoline group and the benzyl group. Scheme II uses a methylene oxide bridge between the two groups and Scheme III uses a triphenyl phosphine reactant similar to Yan. Thus, Oatis does not disclose or suggest the presently claimed invention.

Harris discloses various techniques of making 6-substituted 2,4-diaminoquinazolines. A review of Harris did not reveal the use of triethyl phosphite or any other type of modified Horner reagent. Accordingly, Harris neither discloses nor renders obvious the presently claimed invention.

Vaidya discloses various substituted quinazoline compounds. However, a review of Scheme 1 and Scheme 2 at page 1692 reveals that Vaidya does not disclose or suggest the use of a triethyl phosphite reagent to produce the novel intermediate or otherwise disclose or suggest the improved process of the presently claimed invention.

In view of the foregoing, reconsideration and withdrawal of the anticipation rejections are respectfully solicited.

Claim Rejections Under 35 U.S.C. § 103(a)

Paragraph 20 of the Office Action rejects original claim 1 under 35 U.S.C. § 103(a) as being unpatentable over Nair U.S. Patent 5,912,251 ("Nair"). The rejection focused on the language of original claim 1 which has been revised significantly in independent claim 3. Although Nair may produce a compound within Formula Ib of the present invention, Nair does so in a completely different manner. There is no teaching or suggestion in Nair of using either step of the improved process involving triethyl phosphite or the novel intermediate formed using that modified Horner reagent to produce the compound of Formula Ib. One skilled in the art

would have no motivation to revise Nair's process to Applicants' improved process without a teaching or even a hint to do so, other than the hindsight provided in the present application, which cannot be relied upon as support for a rejection. Accordingly, reconsideration and withdrawal of the obviousness rejection in view of Nair is respectfully solicited.

Paragraph 21 of the Office Action is a provisional double patenting rejection based on claim 1 of copending Application No. 10/627,485, assigned to the assignee of the present application. In view of the amendments to the claims of the present application, it is believed that the double patenting rejection is also overcome. Reconsideration and withdrawal of the double patenting rejection is respectfully solicited.

Conclusion

Accompanying this Amendment is an Information Disclosure Statement including two references for consideration by the Examiner. The references are not believed to render the presently claimed invention unpatentable.

Also accompanying this Amendment is a Revocation and Appointment of Attorney by Assignee. Mr. Dodd, former in-house Senior Patent Counsel for Applicants' assignee, is no longer employed by the assignee. Accordingly, until further notice, further communications should be directed to the undersigned attorney. If advancement of the prosecution of this application could be enhanced by a telephone conference between the Examiner and the undersigned attorney, the Examiner is invited to so contact the undersigned attorney at the Examiner's convenience.

Reconsideration and withdrawal of the rejections and an early Notice of Allowance are respectfully solicited.

Respectfully submitted,

YE WU *et al.*

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Information Disclosure Statement, Form PTO/SB/08A, and references listed thereon;
Revocation and Appointment of Attorney by Assignee.